(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C, and

further wherein transfection efficiency is increased by at least 50%.

REMARKS

The Invention

The present invention relates to methods for introducing a nucleic acid encoding a foreign gene into cells in a patient, wherein transfection efficiency is increased by at least 50%. The methods involve administering a cell cycle blocking agent to the patient and administering the nucleic acid to the patient after administering the cell cycle blocking agent. The cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid. The invention further relates to cancer therapy and, in particular, to methods of introducing nucleic acids encoding foreign genes into a cell in a patient having cancer.

Status of the Claims and Specification

After entry of this amendment, claims 38-44, 47-51, and 69-87 are pending. Claims 38-44, 47-51, and 69-87 stand rejected,in various combinations, under 35 U.S.C. § 112, 35 U.S.C. § 102(b), and 35 U.S.C. § 103(a). These rejections are

addressed below. Claims 52-54 have been canceled without prejudice to future prosecution.

Claims 38, 69, and 74 have been amended to clarify the order of administration of the cell cycle blocker and the nucleic acid. Support for these amendments is found throughout the specification as filed (*see, e.g.*, page 9, lines 23-25 and page 19, line 17-26). Thus, these amendments do not introduce new matter.

In accordance with the Examiner's suggestion, the specification has been amended at page 15, line 26 to recite "Gene Directed Enzyme Prodrug Therapy ("GDEPT")"in place of "GDEPT." It was well known in the art at the time of filing that the acronym GDEPT stood for Gene Directed Enzyme Prodrug Therapy (*see, e.g.*, Connors and Knox, *Stem Cells* 13(5):501-11 (1995), abstract and Connors, *Gene Ther.* 2(10): 702-9 (1995), abstract, copies enclosed as Exhibit B). Thus, no new matter is added by this amendment.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Objection To Claim 42

Claim 42 is objected to for the recitation of the acronym GDEPT. In accordance with the Examiner's suggestion, Applicants have amended the specification at the first presentation of the recited term (*i.e.*, the paragraph beginning at page 15, line 11) to recite "Gene Directed Enzyme Prodrug Therapy ("GDEPT")." Accordingly, Applicant respectfully request withdrawal of this objection.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 38-44, 47-54 and 78-84 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

In making this rejection, the Examiner acknowledge that the claims are enabled for "methods of introducing a nucleic acid encoding a foreign gene and of inhibiting the growth of cancer cells comprising the steps of: (a) first, administering a cell

cycle blocking agent; and (b) second administering a nucleic acid, but alleges that undue experimentation is required for administering the nucleic acid before the cell cycle blocking agent. To expedite prosecution, the claims have been amended to recite that the cell cycle blocking agent is administered before the nucleic acid. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 38-44, 47-52, 69-73, 79-81, and 84-86 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Son *et al.*, *Proc. Natl. Acad. Sci.* (1994), 91:12669-12672.

As explained previously, for a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g.*, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be ***no difference*** between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

The present claims are directed to methods for introducing a nucleic acid encoding a foreign gene into cells in a patient by first administering a cell cycle blocking agent to the patient and second administering the nucleic acid to the patient, whereby transfection efficiency is increased by at least 50%. The cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid.

Son *et al.* is cited a teaching that cell cycle blocking agents can increase transfection efficiency by at least 50%. As explained by Dr. Ian MacLachlan, Son *et al.* disclose that only one cell cycle blocking agent, *i.e.*, cisplatin, was effective in sensitizing cells to transfection (*see*, Declaration ¶ 7). Son *et al.* explicitly states that "only cisplatin could significantly sensitize the tumor for *in situ* lipofection" (page 12671, right hand column). Son *et al.* also present data showing that only cisplatin sensitizes tumors for *in situ* lipofection (Fig. 4). Moreover, as pointed out by Dr. MacLachlan, Son *et al.* teach that ***several*** other anticancer drugs such as methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and carboplatin (a geometric isomer of cisplatin) had no effect on transfection (*see*, Declaration ¶ 7). Son *et al.*'s own interpretation of the data presented in Figure 4 explicitly states that:

> Fig. 4 shows that only cisplatin could significantly sensitize the tumor for *in situ* lipofection. Other anticancer drugs including methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and vincristine had no effect. Transplatin, a geometric isomer of cisplatin that has no anticancer activity also showed no effect.

Thus, Dr. MacLachlan concludes that based on Son *et al.*'s explicit statements, the cited reference does not disclose all of the elements the present invention because, in contrast to the claimed invention, Son *et al.* teach only cisplatin would be useful for methods of introducing a nucleic acid into cells in patient (*see*, Declaration ¶7).

Thus, Son *et al.* fail to disclose all of the elements of the claimed methods of introducing a nucleic acid to cells in a patient using the cell cycle blocking agents recited in the claims (*i.e.*, cyclophosphamide, taxol, taxolene, and a vinca alkaloid), and do not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The claims are rejected, in various combinations, under 35 U.S.C. § 103(a) over a number of different references. As explained previously, to establish a *prima facie*

case of obviousness, (1) there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. (*See*, M.P.E.P., § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

1. Rejection of claims 38,-44, 47, 54, 69-73, 79-81, and 83-86 over Son *et al.* and Roth *et al.*

Claims 38,-44, 47, 54, 69-73, 79-81, and 83-86 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.* and Roth *et al.* (U.S. Patent No. 5,747,469). In making the rejection, the Examiner alleges that Son *et al.* teach that other agents besides cisplatin increase transfection efficiency.

As discussed in detail above in connection with the 35 U.S.C. § 102(b) rejection and in ¶7 of Dr. Ian MacLachlan's declaration, Son *et al.* does not disclose all of the elements, features or limitations of the presently claimed invention because, in contrast to the present invention, Son *et al.* teach away from the use of drugs other than cisplatin to enhance transfection efficiency. For example, as explained in Dr. MacLachlan's declaration, Son *et al.* explicitly states that ***only*** cisplatin significantly sensitizes tumor cells for transfection and that other anticancer drugs, including vincristine, have no effect on transfection efficiency (*see*, Declaration ¶7). As Dr. MacLachlan's declaration points out, Son *et al.*'s interpretation of their own data explicitly states that: "Fig. 4 shows that only cisplatin could significantly sensitize the tumor for in situ lipofection. Other anticancer drugs including methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and vincristine had no effect. Transplatin, a geometric isomer of cisplatin that has no anticancer activity also showed no effect" (*see*, Declaration ¶7). Thus, if anything, Son *et al.* teach away from the present invention. In view of the teachings of

Son *et al.*, one of skill in the art would have ***no motivation*** to use any drug except cisplatin to improve transfection efficiency. Thus, if anything, Son *et al.* teach away from the use of the compounds recited in the claimed invention (*e.g.*, cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid).

As explained by Dr. MacLachlan, Roth *et al.* does not remedy the defect in Son *et al.* (*see*, Declaration ¶8 and ¶11). In contrast to the claimed invention, Roth *et al.* disclose contacting cells with agents such as cisplatin, doxorubicin, etoposide, verapamil, podophyllotoxin, and 5-fluorouracil (*see,* claims 4, 6, 8, 10, 11, and 12, respectively). Roth *et al.* thus fail to disclose the use of any of the cell cycle blocking agents recited in the claims of the present invention. Therefore, as Dr. MacLachlan concludes, even if the teachings of Son *et al.* and Roth *et al.* were combined, the combination would not lead to the claimed invention because the references, either alone or in combination, fail to teach or suggest introducing a nucleic acid encoding a foreign gene into a cell in a patient by administering any of the cell cycle blocking agents (*e.g.*, cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid) recited in the present claims (*see*, Declaration ¶11).

Absent a teaching or suggestion of a method of introducing a nucleic acid into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Therefore, Applicants respectfully request withdrawal of this rejection.

2. Rejection of claims 38-44, 47-54, 69-73, and 78-86 over Son *et al.*, Roth *et al.*, and Walker *et al.*

Claims 38-44, 47-54, 69-73, and 78-86 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.*, Roth *et al.*, and Walker *et al.* (U.S. Patent 6,041,252). In making the rejection, the Examiner alleges that Walker *et al.* disclose general methods for improving the delivery of liposomal compositions and concludes that one of skill in the art would be motivated by Son *et al.* to use any delivery method conventional in the art.

As discussed in detail above and in Dr. MacLachlan's declaration, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* because Son *et al.* teach away from the claimed invention (*see*, Declaration ¶7, ¶8, and ¶11). In particular, Son *et al.* teach that only cisplatin sensitizes tumor cells for transfection and that other anticancer drugs have no effect on transfection efficiency. Moreover, as Dr. MacLachlan explains, even if Son *et al.* and Roth *et al.* were combined, the combination would not lead to the claimed invention because the combination of Son *et al.* and Roth *et al.* does not disclose any of the cell cycle blocking agents recited in the present claims (*see*, Declaration ¶11). Walker *et al.* do not cure the deficiency of Son *et al.* and Roth *et al.* As explained by Dr. MacLachlan, Walker *et al.* disclose the use of electrical fields to deliver therapeutic agents encapsulated in a liposome (*see*, Declaration ¶9). Walker *et al.* explicitly states that the encapsulated agents are used to directly kill tumor cells and that "agents are administered in multiple cycles to kill cells as they enter the correct cell cycle phase" (*see,* col. 36, lines 15-19). Walker *et al.* contains no mention or suggestion of the use of any cell blocker or the introduction of a nucleic acid into a cell. Walker *et al.* does not even contain the words "nucleic acid." Therefore, Dr. MacLachlan concludes that one of skill in the art would not have had the motivation to combine Walker *et al.* with Son *et al.* and Roth *et al.* (*see*, Declaration ¶9 and ¶12). Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Walker *et al.*, the combination would not lead to the claimed method of introducing a nucleic acid into cells in a patient.

Absent a teaching or suggestion of a method of introducing a nucleic acid encoding a foreign gene into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Therefore, Applicants respectfully request withdrawal of this rejection.

3. Rejection of claims 74-77 and 87 over Son *et al.*, Roth *et al.*, and Bally *et al.*

Claims 74-77 and 87 are rejected under 35 U.S.C. § 103(a) as unpatentable over Roth *et al.*, Son *et al.*, and Bally *et al.* (US Patent 5,705,385). In

making this rejection, the Examiner alleges that Bally *et al.* teach general methods for improving gene delivery methods and that Son *et al.* provides motivation for one of skill in the art to optimize gene delivery protocols. Applicants respectfully traverse this rejection.

As discussed in detail above and in Dr. MacLachlan's declaration, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* because Son *et al.* teach away from the claimed invention (*see*, Declaration ¶7, ¶8, and ¶11). In particular, Son *et al.* teach that only cisplatin sensitizes tumor cells for transfection and that other anticancer drugs have no effect on transfection efficiency. Moreover, even if Son *et al.* and Roth *et al.* were combined, the combination would not lead to the claimed invention because the combination of Son *et al.* and Roth *et al.* does not disclose any of the cell cycle blocking agents recited in the present claims. Dr. MacLachlan explains that Bally *et al.* fail to cure this deficiency (*see*, Declaration ¶13). Bally *et al.* does not disclose the use of ***any*** claimed cell cycle blocking agents: cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. Moreover, as Dr. MacLachlan points out, there is no mention or suggestion in Bally *et al.* of the use of a cell cycle blocking agent (*see*, Declaration ¶10 and ¶13). Therefore, as explained by Dr. MacLachlan, one of skill in the art would not have had the motivation to combine Bally *et al.* with Son *et al.* and Roth *et al.* (*see*, Declaration ¶13). Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Bally, *et al.*, the combination would not lead to the claimed method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, by administering the cell cycle blocking agents recited in the present claims.

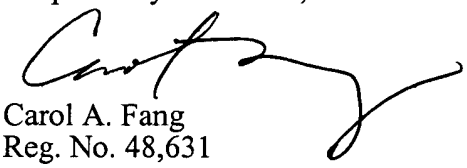
Absent a teaching or suggestion of a method of introducing a nucleic acid encoding a foreign gene into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please insert the following replacement paragraph starting at page 16, line 11.

A "therapeutic gene" is one whose gene product performs a clinically useful function. For example, where the therapeutic gene is used to transform cancer cells, the therapeutic gene will inhibit the growth of the cancer cells. The therapeutic gene is preferably one whose gene product has low toxicity to non-target tissues, and high toxicity to the disease (*e.g.* cancer) site. For example, when delivered in the preferred lipid-nucleic acid (*e.g.*, lipid-plasmid particles) particles of the invention, the gene product preferably has greater toxicity to tumor cells than liver or spleen cells, where a large portion of particles can normally be cleared. Alternatively, a therapeutic gene may be delivered to a treatment site, which is not a disease site, but which activates an immunologic or other response which is then favorable for the amelioration of the disease or disorder being treated. Examples of therapeutic genes useful in the methods of the present invention include, but are not limited to, genes for: pro-apoptotic proteins; tumor suppressors (*e.g.*, p53, Rb1 (Retinoblastoma), *etc.*); cytokines (such as Interleukin-2, Interleukin-12, *etc.*); heat shock proteins; immunogenic antigens (such as tumor-specific proteins, *etc.*); genes activated in embryos only; Endostatin, Angiostatin, Thrombospondin, and other inhibitors of angiogenesis; Enzymes used in [GDEPT] Gene Directed Enzyme Prodrug Therapy ("GDEPT") combinations (*i.e.*, suicide genes used in conjunction with a non-toxic pro-drug), such as Thymidine Kinase from Herpes simplex virus (HSV-TK); cytosine deaminase; porfirin; TIMP-2 (tissue inhibitor of metallo proteinase-2); plant, bacterial or fungal toxin genes, such as saporin, ricin, diphtheria toxin, cholera toxin; viral protein genes, such as E1A; mutated E6; SV40 Tag or viral protein genes which effect plasmid maintenance and/or copy number, such as EBNA-1; transcription plasmids encoding ribozymes or antisense oligonucleotides, Adenosine Deaminase; CFTR - Cystic Fibrosis; GM-CSF, IL-4, IL-2, IL-7, IL-10; Carcineombryonic Antigen; HLA-B7; TNF; T-Cell Receptor Antibody; CEA; Ig; IFN-g;

MART-1; Chimeric Antibody/TCR; Prostate Specific Antigen; anti-erbB-2; Single Chain Antibody; BRCA-1; Alpha-1 Antitrypsin; p47 phax; Fanconi Anemia Complementation Group C; Glucocerbrosidase; Iduronato-2-Sulfatase; Purine Nulceaside Phosphorylase. Other therapeutic genes are continually being discovered and can be used in the methods of the present invention. Therapeutic genes are generally delivered as part of an expression construct, although other formats are possible.

IN THE CLAIMS

38. (Four times amended) A method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, said method comprising the steps of

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein transfection efficiency is increased by at least 50%.

52. (Canceled)

53. (Canceled)

54. (Canceled)

69. (Twice Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in a patient having cancer, said method comprising the steps of:

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered systemically, and wherein transfection efficiency is increased by at least 50%.

74. (Twice Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in said patient, said method comprising the steps of:

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C, and

further wherein transfection efficiency is increased by at least 50%.

APPENDIX B

PENDING CLAIMS

38. (Four times amended) A method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, said method comprising the steps of

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein transfection efficiency is increased by at least 50%.

39. (As filed) The method of claim 38 wherein step (b) is performed within 3 days of step (a)

40. (As filed) The method of claim 38 wherein step (b) is performed within 24 hours of step (a).

41. (Once Amended) The method of claim 38 wherein said foreign gene is a plasmid.

42. (Once amended) The method of claim 38 wherein said foreign gene comprises a gene selected from the group consisting of genes encoding a cytokine, apoptotic protein, tumor suppressor, heat shock protein, immunogenic antigen, proteinase inhibitor, anti-angiogenic protein, suicide gene for use in GDEPT, ribozyme, antisense nucleic acid, viral protein and a toxin.

43. (Once amended) The method of claim 38 wherein said foreign gene is administered systemically.

44. (Once amended) The method of claim 38 wherein said foreign gene is administered locally or regionally.

47. (Once Amended) The method of claim 38, wherein said cell cycle blocking agent is selected from the group consisting of cyclophosphamide, taxol, and vincristine.

48. (As filed) The method of claim 38 wherein said cell cycle blocking agent is in a liposome formulation.

49. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered prior to administering said foreign gene.

50. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 32 h prior to administering said foreign gene.

51. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 48 h prior to administering said foreign gene.

69. (Twice Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in a patient having cancer, said method comprising the steps of:

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered systemically, and wherein transfection efficiency is increased by at least 50%.

70. (As filed) The method of claim 69, wherein said cancer comprises a tumor.

71. (Once amended) The method of claim 70, wherein said cell cycle blocking agent and said foreign gene are administered distal to the site of the tumor.

72. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign gene are administered intravenously.

73. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign gene are administered intraperitoneally.

74. (Twice Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in said patient, said method comprising the steps of:

(a) first administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) second administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C, and

further wherein transfection efficiency is increased by at least 50%.

75. (As filed) The method of claim 74, wherein said (PEG)-lipid derivative is a PEG-ceramide.

76. (As filed) The method of claim 75, wherein said PEG-ceramide is a member selected from the group of PEG-Cer-C14, PEG-Cer-C20, and PEG-Cer-C8.

77. (Once Amended) The method of claim 74, wherein said lipid derivative is present in an amount of from about 1% to about 20% by weight of the lipid formulation.

78. (As filed) The method of claim 74, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting said cationic lipid with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

79. (As filed) The method of claim 38, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

80. (As filed) The method of claim 38, wherein the nucleic acid is in a lipid formulation.

81. (As filed) The method of claim 80, wherein the nucleic acid is fully encapsulated in a lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

82. (As filed) The method of claim 80, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting cationic lipids with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

83. (As filed) The method of claim 69, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

84. (As filed) The method of claim 74, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

85. (As filed) The method of claim 38, wherein the foreign gene is a therapeutic gene.

86. (As filed) The method of claim 69, wherein the foreign gene is a therapeutic gene.

87. (As filed) The method of claim 74, wherein the foreign gene is a therapeutic gene.